International Association for Cannabis as Medicine

in cooperation with the
Department of Psychiatry and Psychotherapy and the
Department of Anaesthesiology of the University of Cologne

IACM 2nd Conference on Cannabinoids in Medicine

12-13 September 2003
Cologne
University of Cologne – Medical School

Program and Abstracts

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IACM 2nd Conference on Cannabinoids in Medicine

Place	Centre for Anatomy, University of Cologne – Medical School Joseph-Stelzmann-Straße, 50937 Köln (Cologne)
Registration Fee	25 € (Euros) a day 50 € whole conference Free for members of the IACM and the University of Cologne Free for students and AiP
Organizer	IACM, Arnimstraße 1 A, 50825 Köln Phone: 49-(0)221-95439229 E-mail: info@cannabis-med.org Internet: http://www.cannabis-med.org
Cooperation Partners	Department of Psychiatry and Psychotherapy of the University of Cologne Department of Anaesthesiology of the University of Cologne
Program Committee	Franjo Grotenhermen Markus Leweke Kirsten Mueller-Vahl Lukas Radbruch Rainer Sabatowski Martin Schnelle

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Program - 12 September 2003

08:00-08:30 **Registration**

08:30-08:45 **Greetings**
Raphael Mechoulam (IACM)
Dean of the Medical Faculty

08:45 – 15:00 Lectures & Reviews

08:45-10:20 **First Session** Chair: Richard. Musty, Ester Fride
- 08:45 John Zajicek: Cannabis and dronabinol in multiple sclerosis
- 09:05 William Notcutt: Three years of clinical experience with CBME
- 09:30 Ulrike Hagenbach: The treatment of spasticity with Δ9-tetrahydrocannabinol (Δ9-THC) in patients with spinal cord injury.
- 09:50 Rüdiger Lorenz: Experiences with THC-treatment in children and adolescents
- 10:05 Ricardo Navarrete-Varo: Interview of a group of patients treating themselves with cannabis: Evaluation of the difficulties involved and therapeutic results

10:20-10:45 **Coffee Break**

10:45-11:55 **Second Session** Chair: Rudolf. Brenneisen, Mahmoud ElSohly
- 10:45 Ester Fride: Effects of cannabidiol analogues on intestinal motility: possible application for inflammatory bowel disease
- 11:05 William R Ford: Anandamide limits infarction after ischemia-reperfusion in rat isolated hearts
- 11:20 Jürgen Wolf / Florian Kram: Endogenous cannabinoids increase pulmonary arterial pressure via cyclooxygenase-2 products in isolated rabbit lungs
- 11:40 G. Berding: SPECT studies of central cannabinoid CB1-receptors in Tourette patients using the ligand [123I]AM281 and assessment of the associated radiation exposure based on whole body imaging

12:00-13:00 **Review** Chair: Joachim Klosterkötter
Raphael Mechoulam: The role of the cannabinoid system in neuroprotection

13:00-14:20 **Lunch**

14:20-15:00 **Third Session** Chair: Bela Szabo, Franjo Grotenhermen
- 14:20 Clare Hodges: Information gained from current medicinal users of cannabis for multiple sclerosis
- 14:40 Willem K. Scholten: The production and distribution of cannabis as a highly standardized botanical startiug material

15:00 – 17:45 Workshops

15:00-15:45 **Circulation** Chair: Bela Szabo, Franjo Grotenhermen
with Jens Wagner and Bela Szabo
Bela Szabo: Sites of action of cannabinoids in the cardiovascular system
Jens Wagner: Effects of endogenous cannabinoids on circulation

15:45-16:15 **Coffee Break**

16:15-17:45 **Neurology** Chair: Kirsten Müller-Vahl, Ethan Russo
- 16:15 Bela Szabo: Modulation of synaptic transmission by exogenous and endogenous cannabinoids"
- 16:50 Katerina Venderová: Cannabinoid system as a new target in Parkinson´s disease pharmacotherapy"
- 17:00 Kirsten Müller-Vahl: Cannabinoids in the treatment of movement disorders

17:10 Susanne Luz: Results of a questionnaire at the end point of the THC-study to evaluate the subjective therapeutic effects and side effects of THC in the treatment of spasticity
17:20 Clare Hodges: Psychoactive effects of cannabinoids: beneficial therapeutic or unwanted adverse effects?
17.30 General discussion

17:45 End of the session

19:00 Dinner Hofbräustuben im Früh

Program - 13 September 2003

08:15-08:45 **Registration**

08:45 – 13:00 Lectures & Reviews

08:45-10:20 First Session Chair: Donald Abrams, Florian Strasser
08:45 Raphael Mechoulam: Bone formation: a novel aspect of cannabinoid action
09:05 Ethan Russo: Cannabis improves night vision: a pilot study of visual threshold and dark adaptometry in kif smokers in the Rif region in northern Morocco
09:25 Michael P Schaub: Goals of cannabis use in students: a multifactorial model and its association with schizotypal traits
09:40 Peter Fried: Does sex matter? A within- and between-subject longitudinal assessment of marihuana's impact and memory and processing speed
10:00 Florian Strasser: Oral cannabis - extract (CE) versus delta-9-tetrahydrocannabinol (THC) for patients with cancer-related anorexia (CRA): A randomized, double-blind, placebo-controlled, multicenter study

10:15-10:45 Coffee Break

10:45-11:55 Second Session Chair: William Notcutt, Ulrike Hagenbach
10:45 Martin Schnelle: Maximally tolerated dose (MTD) of standardized cannabis extract in palliative cancer patients: preliminary results from an open-label, non-randomized phase I/II trial
11:00 Dale Gieringer: Cannabis vaporizer combines efficient delivery of THC with effective suppression on pyrolytic compounds
11:20 Mahmoud A. ElSohly: A suppository formulation for delivery of Δ9-THC using a prodrug
11:35 Kateřina Venderová: Urine levels of 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid in Parkinson's disease patients using cannabis

12:00-13:00 Review Chair: Walter Buzello
Vincenzo Di Marzo: Possible use of endocannabinoid-based therapeutic drugs against tumour growth and metastatic spreading

13:00-14:15 Lunch

14:15 – 18:00 Workshops

14:15-16:00 Pain Chair: Gernot Ernst, Lukas Radbruch
Birgit Kraft: Cannabinoid analgesia - animal models and clinical results
Udo Schneider: Analgesic effects of 1`,1`dimethylheptyl-delta8-THC-11-oic acid (CT-3) on chronic neuropathic pain in man.
Anita Holdcroft: An escalating dose study of cannador for postoperative pain: dose related effects

Frank Elsner: Use of cannabinoids in palliative care
Donald I. Abrams: The effects of smoked cannabis in painful peripheral neuropathy and cancer pain refractory to opioids

16:00-16:30 Coffee Break

16:30-18:00 Psychiatry Chair: F. Markus Leweke, Don Linszen

16:30 F. Markus Leweke: Endogenous cannabinoids and their role in psychiatric disorders
16:45 Richard E. Musty: Cannabidiol, Δ^9-tetrahydrocannabinol, and cannabichromene extracts alter behavioral despair on the mouse tail supension test of depression
17:05 A. Stadelmann:
17:20 C. Henquet: Cannabis use and psychosis in adolescents and young adults
17:40 Don H Linszen: Cannabis use: challenging vulnerabilities in schizophrenia. The Amsterdam experience

18:00 End of the conference

THE TREATMENT OF SPASTICITY WITH Δ^9-TETRAHYDROCANNABINOL (Δ^9-THC) IN PATIENTS WITH SPINAL CORD INJURY (SCI)

Ulrike Hagenbach[1], Susanne Luz[1], Rudolf Brenneisen[2], Mark Mäder[1].

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[2]Department of Clinical Research, University of Berne, 3010 Berne, Switzerland

Introduction:
Spasticity is a common complaint after traumatic SCI. Δ^9–THC the main psychoactive cannabinoid of cannabis has been shown to have beneficial effects in the treatment of spasticity of different origin. The aim of the study was to assess the effectiveness and safety of Δ^9–THC (Dronabinol, Marinol® capsules) and THC-hemisuccinate suppositories (THC-HS) for the treatment of spasticity in patients with SCI as a homogeneous population of patients. We are presenting the results of spasticity as partial results of a finished study with a wide spectrum of other investigations.

Methods:
Phase 1: open trial, six weeks treatment of 22 patients with Dronabinol (7 drop outs)
Phase 2: open trial, six weeks treatment of 8 patients with THC-HS (1 drop out)
Phase 3: randomized, double-blind, placebo controlled clinical trial with 13 patients (Marinol®/placebo)
25 patients mean age 42.3 years with spasticity due to SCI (11 para- and 14 tetraplegics) were included. Mean time since injury was 13.4 years. Inclusion criteria for spasticity were minimum of 3 points on the Ashworth scale without therapy, negative urine drug screening, age > 18 years.
Spasticity was investigated using the modified Ashworth scale (MAS) after administration of 10 mg Dronabinol (Marinol®) or 10 mg THC-HS at day one and after one and six weeks treatment with an individual dose. Self-rating of spasticity was performed every day using a seven point scale from absent to unbearable.

Results:
Phase 1: Dronabinol (Marinol®) significantly decreased the mean spasticity sum score (± SD) (summed Ashworth scores divided by four) in 15 patients after a single dose of 10 mg (day 1) from 16.72 ± 7.60 to 7.75 ± 7.00 points ($p<0.001$) and after 6 weeks of treatment with an individual symptom oriented mean dose of 30 mg Dronabinol to 8.92 ± 7.14 points ($p<0.05$).
Phase 2: THC-HS significantly decreased the mean spasticity sum score (± SD) in 7 patients after a single dose of 10 mg (day 1) from 22.71 ± 11.68 to 9.86 ± 8.15 points ($p<0,05$) and after 6 weeks of treatment with an individual symptom oriented mean dose of 43 mg THC-HS to 9.21 ± 9.25 points ($p<0.05$).
The comparison of oral and rectal application in five patients showed no difference.
Phase 3: summed spasticity scores for the Dronabinol group (7.21 points) differed significantly from summed scores of the placebo group (12.10 points) as a treatment effect of Dronabinol during the entire 6 weeks ($p=0.001$).

Conclusion:
The results demonstrate a significant therapeutic effect of Δ^9–THC (Dronabinol, Marinol ®) as well as THC-HS in patients with SCI. However the antispastic efficacy is significant the treatment often is limited by side effects.

Acknowledgement:
The research was supported by ElSohly Laboratories Inc., Oxford, Mississippi

EXPERIENCES WITH THC-TREATMENT IN CHILDREN AND ADOLESCENTS

Rüdiger Lorenz

Paediatrician, Brunnenstrasse 54, 34537 Bad Wildungen, Germany

8 patients – children or adolescents aged 3 to 14 years – have been treated with Δ^9-THC, dosages ranged from 0.04 mg/kg body weight to 0.14 mg/kg body weight.

In an 8 year-old-boy with NCL Jansky-Bielschowsky spasticity was diminished, he became more alert and his mood improved.

In a 12 year-old-girl, who had suffered from severe hypoxia during birth, mood improved, awareness was increased and focal seizures (presenting as nystagmus and versive movement) but not tonic-clonic seizures were reduced.

A 12 year-old-girl with PDHC-deficiency became more interested in her surroundings and society. Nodding spasms and tonic seizures decreased.

In a 14 year-old-girl with marked dystonia due to NCL Spielmeyer-Vogt a reduction of abnormal movement patterns was observed. In addition the girl had more initiative.

In a 13 year-old-boy presenting with spasticity, athetosis, myoclonic movements and epileptic seizures of unknown cause interest in his surroundings was improved, myoclonic movements were less intense but of similar frequency. Frequency and duration of his focal and generalized seizures were not influenced.

In an 11 year-old-girl with a traumatic paraplegia a significant improvement of symptoms of a posttraumatic reaction presenting as an eating disorder and negative behaviour was observed. Taking higher doses the girl started to develop side effects including inappropriate language (concerning sexual content) and very associative thinking. Therapy was discontinued without signs of withdrawal.

In a 3 10/12 year-old-boy with a traumatic paraplegia a significant improvement in his behaviour and eating disorder was observed.

In a 14 year-old-boy suffering from intractable epilepsy and severe mental retardation appetite and mood improved. Frequency of seizures seemed not to be influenced, but clear assessment was not possible because antiepileptic drugs were changed.

Conclusion: In severly disabled children and adolescents Δ^9-THC-medication can have positive psychotropic effects, influences the degree of spasticity and dystonia and-occasionally-seems to have an anticonvulsant action.

INTERVIEW OF A GROUP OF PATIENTS TREATING THEMSELVES WITH CANNABIS: EVALUATION OF THE DIFFICULTIES INVOLVED AND THERAPEUTIC RESULTS

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Introduction: For years the vegetable extract of the plant commonly known as cannabis (*cannabis sativa*) has been used to treat many diseases. The discovery of the main active ingredient, delta-9-tetrahydrocannabinol (THC), the finding of the natural system of endocannabinoid neurotransmission and the determination of its important function as a modulator of many physiological functions have shown that the original empiric use is based on solid scientific principles. Among the best established therapeutic properties of THC are its antiemetic effect and its ability to control muscle spasms. Despite the fact that this plant is still illegal, many patients admit consuming cannabis or its extracts to alleviate their symptoms, even though this very status involves inconveniences. We undertook a minimum participation qualitative analysis of the therapeutic use of cannabis in a group of patients to determine the benefits, side effects, and difficulties involved considering its legal status in Spain and propose corrective measures.

Material and methods: The theoretical sample method was used to select a group of patients who acknowledged consuming or having consumed cannabis or its extracts to control the symptoms of their diseases. Patients were followed using semi-structured personalised interviews. We present four patients who consumed cannabis, one to control symptoms of multiple sclerosis and three to control vomiting caused by chemotherapy for breast cancer (1 case) or ovarian cancer (2 cases).

Results: The patients interviewed considered the risk-benefit ratio worthwhile for the therapeutic use of cannabis. They reported satisfactory control of their symptoms which enabled them to reduce the dosage of their regular medication, thereby minimising the risk of intolerance and side-effects. They all agreed that their quality of life was improved by cannabis consumption. The side-effects were minimal and well-tolerated. The main difficulties found by the patients involved the impossibility of sharing opinions with their doctors, the acquisition of the necessary information to evaluate the best mode of consumption in order to minimise risks and gain the greatest therapeutic benefit, and obtaining cannabis with a sufficient degree of quality and standardisation.

Conclusion: There is a general lack of studies evaluating the clinical use of cannabis and its extracts, especially concerning its long-term side effects. Qualitative evaluation by means of interviews appears to be a simple efficient method to evaluate the relevance of more complex placebo-controlled trials in clinical situations where conventional drugs fail to provide the expected benefits. As a model for researchers and patients for the standardized supply of cannabis in Spain we propose the adoption of the protocol followed by the Dutch Ministry of Health Office of Medicinal Cannabis.

Acknowledgements: José Miguel Morales Asensio, Head of Investigation, Malaga Health District, for technical advice.

EFFECTS OF CANNABIDIOL ANALOGUES ON INTESTINAL MOTILITY: POSSIBLE APPLICATION FOR INFLAMMATORY BOWEL DISEASE

Ester Fride[1,2], Cfir Feigin[1], Datta Ponde[3], Aviva Breuer[3], Lumír Hanuš[3] and Raphael Mechoulam[3]

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The two major constituents of the *cannabis sativa* plant, delta-9 tetrahydrocannabinol (Δ9-THC) and (-) cannabidiol (CBD) have very different pharmacological profiles: Δ9-THC activates CB1 and CB2 receptors and induces psychoactive and peripheral effects. CBD does not bind CB1 or CB2 receptors, yet shares some activities with Δ9-THC. Therefore, CBD or its derivatives may be developed for the treatment of a number of conditions such as inflammation, inflammatory pain and diarrhea, in which cannabinoids have therapeutic potential, but where central cannabimimetic effects are undesirable. We have tested a series of previously synthesized (+) and (-)CBD analogues (*Bisogno et al., Br. J. Pharm. 2001;134:845-852*) in mice, both for central and for peripheral activity, as measured by intestinal motility. The compounds included the natural (-)CBD, the synthetic isomer (+)CBD and several (-) and (+) analogues: (-) and (+) CBD-DMH, (+) 7OH-CBD, (-) and (+) 7OH-CBD-DMH, (-) and (+) COOH-CBD and (-) and (+) COOH-CBD-DMH.

Methods: Female Sabra mice, or $CB1^{-/-}$ knockouts were injected *i.p.* 1 hr before testing in a series of assays which assess central cannabimimetic activity and for intestinal motility. Hypothermia and intestinal motility were measured for a prolonged period (4 h). Antagonists, when used, were injected 30 min before the agonist. Peripheral pain was measured as the response to an injection of formalin (4%) in one of the hind paws.

Results: **1)** None of the (-)CBD analogues had any central cannabimimetic effect, yet **2)** all except (-)COOH-CBD, and (-)CBD itself, inhibited intestinal motility. **3)** The (+) derivatives, except (+) CBD itself, bind CB1 and to a lesser extent, CB2 receptors. However, only (+)7OH-CBD-DMH was centrally active. **4)** (+)7OH-CBD-DMH had no effects in $CB^{-/-}$ mice. **5)** All (+)CBD derivatives induced a complete arrest of defecation, except (+)CBD itself. **6)** All effects of (+) CBD-DMH and (+) 7OH CBD-DMH were antagonized by the CB1 receptor antagonist SR141716A, but **7)** not by the CB2 antagonist SR144528. **8)** The vanilloid 1 (VR1) receptor antagonist, capsazepine, did not antagonize any of the effects, thus excluding VR1 receptors as a target for the intestinal effects of CBDs. (+) CBD analogues completely suppressed the inflammatory phase of formalin-induced pain.

Conclusions: We conclude from these findings, that **a**) the effects of the CB-receptor- binding (+)CBD analogues are mediated by CB1 receptors. **b)** (+)CBD-DMH, despite its high affinity for CB1 receptors, was not centrally active, possibly due to a mixed agonist/antagonist potential. **c**) The effects on intestinal motility of the CBD analogues are not mediated by CB2 or VR1 receptors. **d)** Activity of non-CB1, non-CB2 binding CBD analogues, in intestinal motility, suggests the mediation by an unknown receptor in the intestinal system. **e)** Finally, some of the CBD analogues devoid of central effects show therapeutic potential as anti-inflammatory drugs for the GI system, with application in conditions such as Inflammatory Bowel disease and Crohn's disease.

ANANDAMIDE LIMITS INFARCTION AFTER ISCHAEMIA-REPERFUSION IN RAT ISOLATED HEARTS.

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Evidence suggests that endocannabinoids, such as anandamide, might limit infarction associated with myocardial ischaemia-reperfusion (IR). Briefly, CB_2 receptors have been shown to play a role in limiting infarction after IR due to lipopolysaccharide (*Lamontagne et al., Br J Pharmacol 2001; 132: 793-6*) or heat stress (*Joyeaux et al., Cardiovasc Res 2002; 55: 619-25*) pre-treatment. In addition, the synthetic cannabinoid, HU-210, reduces the area of necrosis following IR (*Ugdyzhekova et al., Bull Exp Biol Med 2002; 133: 125-6*). The aim of our study was to determine whether anandamide could itself limit infarction induced by IR, and if so, whether CB_1 or CB_2 receptors were involved in mechanism of protection.

Hearts, removed from male Wistar rats (300-400g) that were heparinized (100 U/kg i.p.) and killed with an overdose of sodium pentobarbitone, were perfused at a constant pressure (80 mmHg) with a modified Krebs-Henseleit solution containing 100 mU/l insulin. The temperature of the perfusate was maintained at 37^{o}C and continuously bubbled with a 95% O_2/ 5% CO_2 gas mixture. During periods of aerobic perfusion, hearts were electrically paced at 300 bpm. Left ventricular developed pressure (LVDP) was measured by means of a pressurised balloon placed in the left ventricle. Coronary flow was measured by means of ultrasonic flow probes. Hearts were randomly assigned to one of five experimental groups: Vehicle (1:4 soya oil: water mixture emulsified with polozamer F188), anandamide (1 μM), anandamide (1 μM) + SR141716A (1 μM, dissolved in DMSO), anandamide (1 μM) + SR144528 (1 μM, dissolved in DMSO) or SR141716A + SR144528 (1 μM each, dissolved in DMSO). Antagonists, where used, were present in the perfusate throughout the perfusion. Anandamide or its vehicle, was infused for 5 min before 30 min of global, no-flow ischaemia was initiated. After ischaemia, anandamide or its vehicle was infused throughout the 2 h of reperfusion. At the end of reperfusion, infarct size was determined by staining with a 1% solution of triphenyltetrazolium chloride. Data are expressed as means ± S.E.M. Statistical analysis was carried out using ANOVA supported by Dunnett's *post hoc* test.

Baseline parameters of LVDP and coronary flow did not vary among any of the experimental groups. After 2 h reperfusion in vehicle treated hearts (n=12), LVDP and coronary flow recovered incompletely (27±4% and 19±4% of pre-ischaemic values, respectively). The recoveries of LVDP and coronary flow during reperfusion did not significantly vary among any of the other experimental groups. In vehicle-treated hearts, infarct size was 20±2% of the left ventricle. Compared to vehicle treated hearts, anandamide (n=11) significantly reduced infarct size (11±1% of the left ventricle). The protection afforded by anandamide was abolished by co-treatment with SR141716A (n=12) or SR144528 (n=14) the values being 20±3% and 21±2% of the left ventricle, respectively. Treatment with the combination of SR141716A and SR144528 (n=5) did not significantly affect infarct size (24±4% of the left ventricle).

In conclusion, anandamide limits myocardial infarction associated with IR. One possible mechanism of action is via interaction with either CB_1 or CB_2 receptors. However, it is interesting that the pharmacological profile fits the recently described (*Ford et al., 2002, Br J Pharmacol; 135: 1191-98*) novel site of anandamide action, distinct from CB_1 or CB_2 receptors, mediating responses in the rat heart.

Acknowledgements: The British Heart Foundation, UK.

ENDOGENOUS CANNABINOIDS INCREASE PULMONARY ARTERIAL PRESSURE VIA CYCLOOXYGENASE-2 PRODUCTS IN ISOLATED RABBIT LUNGS

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Cannabinoids show complex cardiovascular actions. The endocannabinoid arachidonyl ethanolamide (anandamide) induces vasodilation mainly via CB1 cannabinoid receptors. Additionally, VR1 vanilloid receptors or specific "anandamide receptors" may be involved. Using an isolated, ventilated, recirculating buffer-perfused rabbit lung model, we show that the endocannabinoids anandamide and 2-arachidonyl-glycerol (2-AG) dose-dependently increase pulmonary pressure (19.9 ± 8.3 mmHg, 5 μmol/L, n=6; and 39.5 ± 21.6 mmHg, 0.4 μmol/L, n=4). The specific CB1 receptor antagonist AM-251 (5 μmol/L, n=5), the VR1 receptor antagonist capsazepine (10 μmol/L, n=5) and the synthetic thromboxane receptor antagonist SQ29,548 (0.5 μmol/L, n=4) failed to reduce pulmonary hypertension following anandamide. The metabolically stable anandamide- and 2-AG- analogues, R-methanandamide (5 μmol/L, n=4) and noladin ether (4 μmol/L, n=4), and the synthetic cannabinoid HU-210 (5 μmol/L, n=3), which is no arachidonic acid product, were without effect. The unspecific cyclooxygenase (COX) inhibitor aspirin (0.7 ± 0.3 mmHg, 100 μmol/L) and the specific COX-2 inhibitor nimesulide (1.4 ± 0.7 mmHg, 10 μmol/L), completely prevented pulmonary hypertension following anandamide. The prostanoid EP1 receptor antagonist SC19220 attenuated the pulmonary pressure effect of anandamide (12.4 ± 4.4 mmHg, 100 μmol/L, n=4). PCR analysis detected fatty acid amidohydrolase (FAAH), the enzyme mainly responsible for the degradation of endocannabinoids, in rabbit lung tissue. Further, the specific FAAH inhibitor methyl arachidonyl fluorophosphonate (MAFP, 0,1 μmol/L) attenuated pressure effects of anandamide (0.5 ± 0.3 mmHg, n=5). Finally, anandamide (99 ± 55 pmol/g wt tissue, n=3) and 2-AG (19.6 ± 8.4 nmol/g, n=3), as detected by liquid chromatography / mass spectrometry, were found in native rabbit lungs.

We conclude that anandamide and 2-AG dramatically increase pulmonary pressure via COX-2 metabolites following enzymatic degradation by the FAAH into arachidonic acid products.

SPECT STUDIES OF CENTRAL CANNABINOID CB_1-RECEPTORS IN TOURETTE PATIENTS USING THE LIGAND [^{123}I]AM281 AND ASSESSMENT OF THE ASSOCIATED RADIATION EXPOSURE BASED ON WHOLE BODY IMAGING

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The aims of the present pilot-study were (1) to demonstrate increased in vivo binding of the ligand in areas of the human brain with known high receptor density, (2) to assess its in vivo stability in the blood and (3) to estimate the effective dose induced by its use.

Six patients (mean age 34; 4 males) fulfilling the DSM-VI criteria for Tourette Syndrome and with a mean severity according to Shapiro's scale of 2.3±0.5 were included in the study. Dynamic SPECT acquisition and simultaneous blood sampling commenced immediately after i.v. injection of 200 MBq of the pyrazole derivative [^{123}I]AM281. Region of interest (ROI-)analysis was applied to reconstructed SPECT-tomogramms to detect activity concentrations for the calculation of specific over non-specific binding ratios (V_3''). From whole body images obtained up to 24 h p.i., uptake and effective half life of the tracer in target organs were extracted with ROIs. Organ and effective doses were calculated using the MRIDOSE 3.1 software.

A peak of [^{123}I]AM281 uptake in the brain was noticed in the lentiform nuclei at 30 to 70 min p.i.. For this region specific over non-specific binding ratios of 0.30 were obtained with the occipital cortex as reference. Thin layer chromatography showed 70% of non-metabolised tracer in the blood up to 3 h p.i.. Dose calculations revealed the highest organ doses for the upper large intestine (9 mSv / 200 MBq), the spleen (8 mSv / 200 MBq) and the liver (6 mSv / 200 MBq). An effective dose of 2.3 mSv was determined.

The present study demonstrated an about 30% higher binding of [^{123}I]AM281 to the lentiform nuclei compared to a reference region, which is consistent with a high CB_1-receptor density in these nuclei known from post mortem studies and speaking for specific binding of the ligand. In vivo stability of the tracer in the blood was sufficient. The radiation exposure was in the range of frequently used radiological or nuclear medicine diagnostic procedures. In summary [^{123}I]AM281 appears to be a useful candidate for CB_1-receptor imaging in humans.

THE IMPORTANCE OF CANNABINOIDS IN NEUROPROTECTION

Raphael Mechoulam

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The endocannabinoids anandamide and 2-arachidonoyl-glycerol, as well as some plant and synthetic cannabinoids, exhibit neuroprotective effects after brain injury or ischemia. Cannabinoid receptor agonists inhibit glutamergic synaptic transmission and reduce the production of tumour necrosis factor and reactive oxygen intermediates, which are factors in causing neuronal damage. The formation of the endocannabinoids is strongly enhanced after brain injury, and there is evidence that these compounds reduce the secondary damage incurred. Some plant and synthetic cannabinoids, which do not bind to the cannabinoid receptors, have also been shown to be neuroprotective, possibly through their direct effect on the excitatory glutamate system and/or as antioxidants.

INFORMATION GAINED FROM CURRENT MEDICINAL USERS OF CANNABIS FOR MULTIPLE SCLEROSIS

Clare Hodges

Multiple Sclerosis sufferer and medicinal cannabis user. Since 1993 Director of Alliance for Cannabis Therapeutics (ACT), Leeds LS7 4XF, UK

The ACT has received a large correspondence over the last ten years, including letters from hundreds of medical cannabis users. In order to help his research in 1994 we sent questionnaires to these correspondents to the ACT for Dr. Pertwee of Aberdeen University. Over a hundred people responded to the questionnaires he had devised, and he published the results in European Neurology (Eur Neurol 1997:38:44-48). Almost all patients reported benefits, particularly in spasticity and pain (over 90%). The survey was based on single answers to specific questions. The following observations are more wide-ranging, based on the now much larger correspondence and on many conversations over the years with patients who use cannabis. People with a variety of medical conditions have contacted us, but these observations are based on Multiple Sclerosis.

Psychoactivity. Almost all current cannabis users say that it helps them because it not only eases their physical problems, but because it also lifts their spirits, and improves their quality of life. Most studies concentrate on the physical benefits of cannabis, and it may well be helpful to look at the beneficial psychoactive benefits especially in chronic illnesses.

Delivery Methods. Most patients smoke cannabis, as it is a very efficient way of controlling the dosage. People who do not wish to smoke have been very inventive, from taking it in food, skin patches and suppositories. It seems very important to patients that they have some sort of control over their medication and can self-titrate in the same way that patients can for pain relief. Different delivery methods other than oral should be researched.

Dosage. It is remarkable the very different amounts people use to find relief. For some, an ounce of herbal cannabis may last four months, for others only two weeks. Similarly the amount used can vary considerably in the same patient. Research should be more flexible in amounts tested on patients, acknowledging the variability of the disease.

In general, anecdotal accounts from current users of medicinal cannabis could usefully be investigated further to help direct research.

THE PRODUCTION AND DISTRIBUTION OF CANNABIS AS A HIGHLY STANDARDIZED BOTANICAL STARTING MATERIAL

Willem K. Scholten

Head, Office of Medicinal Cannabis, Ministry of Health, Welfare and Sport, P.O. Box 20350
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The Netherlands will introduce cannabis as a medicine approximately in September 2003. The Office of Medicinal Cannabis(OCM) of the Ministry of Health, Welfare and Sport will distribute it as a starting material for medicines to pharmacies. Introducing cannabis as a pharmaceutical starting material requires high quality standards.

This presentation will focus on the organization of the production and distribution. The requirements set by the Single Convention on narcotic drugs, saying that any state allowing the culture of cannabis has to establish a government agency, having the monopoly on import, export and wholesale and doing the licensing of the growers, will be fully met. The distribution will be operated on a contract base by a pharmaceutical company on behalf of the Office of Medicinal Cannabis.
The presentation will also pay attention on how cannabis can be produced in a reliable way, yielding a highly standardized product: not all cannabis is usable as a pharmaceutical starting material.
Also the background of the decision to make cannabis available as a starting material for medicines and information aspects will be discussed.

If available, first experiences will be presented.

EFFECTS OF ENDOGENOUS CANNABINOIDS ON CIRCULATION

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A brief report of results from our laboratory is given. We summarize how the endogenous cannabinoids anandamide and 2-arachidonylglycerol influence blood pressure and vascular tone under experimental conditions of circulatory (haemorrhagic, septic and cardiogenic) shock. Further, the impact of endogenous cannabinoids on the development of congestive heart failure post myocardial infarction in a rat model is shown. Finally, we report about direct effects of various cannabinoids on human heart muscle.

CANNABINOIDS AND BONE REMODELING

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There are 2 striking features among the multitute of clinical characteristics of osteoporosis: gonadal failure causes bone loss and obesity protects from bone loss. And the peptide leptin is known to negatively regulate both osteoblastic and cannabinoid activity. The role of endocannabinoids in the control of body weight and reproduction as well as its relationships to leptin led us to look at the possibility that the endocannabinoid system is involved in bone remodeling. In initial observations we have noted that reverse polymerase chain reaction of differentiating osteoblastic precursor cells demonstrates progressive increase in mRNA levels of CB2 but not of CB1. In addition normal mice systematically treated with 2-AG or with a specific CB2 agonist showed a dose dependent increase in trabecular bone formation. On the basis of these initial data we assume that endocannabinoids stimulate bone formation.

CANNABIS IMPROVES NIGHT VISION: A PILOT STUDY OF VISUAL THRESHOLD AND DARK ADAPTOMETRY IN KIF SMOKERS IN THE RIF REGION OF NORTHERN MOROCCO

Ethan Russo[1], Abderrahmane Merzouki[2, 3], Joaquín Molero Mesa[2] and Kay Frey[4]

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Psychoactive effects of cannabis have been known for millennia. Interesting claims of lowered visual thresholds after cannabis use have appeared from time to time in the literature. West reported an improvement in night vision among Jamaican fishermen after ingestion of a crude tincture of herbal cannabis (West, *Nature*, 1991, 351, 703-4). More recently, Merzouki and Molero Mesa reported that Moroccan fishermen and local mountain population observe an improvement in night vision after smoking *kif,* sifted cannabis traditionally mixed with tobacco *(Nicotiana rustica)*(Merzouki and Molero Mesa, *Ars Pharmaceutica*, 1999, 40, 233-240). Case reports of improved vision in retinitis pigmentosa after smoking cannabis have appeared (Arnold, *Nursing Standard,* 1998, 12, 17).

Field-testing of night vision has recently become possible with the development of a portable device, the LKC Technologies Scotopic Sensitivity Tester-1 (SST-1) (Gathersburg, MD, USA) (Peters et al., *Doc Ophthalmol,* 2000, 101, 1-9).

This study examines the results of double-blinded graduated THC administration 2.5-20 mg (as Marinol®) vs. placebo in one subject on measures of dark adaptometry and scotopic sensitivity employing the SST-1. Analogous field studies were performed in Morocco with the device in three subjects before and after smoking cannabis. In both test situations, improvements in night vision measures were noted after THC or cannabis. It is believed that this effect is dose-dependent and cannabinoid-mediated at the retinal level (Straiker et al. *Ophthalmol Vis Sci* 1999, 40, 2442-8). Further testing under totally objective conditions with cannabis-based medicine extracts with eletroretinography (ERG) may assess possible clinical application of these results in nyctalopia, retinitis pigmentosa or other clinical conditions.

GOALS OF CANNABIS USE IN STUDENTS: A MULTIFACTORIAL MODEL AND ITS ASSOCIATION WITH SCHIZOTYPAL TRAITS

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PURPOSE: This study aimed at analysing the goals of cannabis use in students regarding schizotypal traits. SAMPLE: One-hundred-ninety-seven psychology students from the Universities of Basel, Berne and Zurich, Switzerland. Of these, 55 students were excluded from further analysis since they had no history of cannabis use.

METHODS: All subjects were recruited through the internet and completed a set of online questionnaires. The first questionnaire assessed demographic and drug use characteristics. The second questionnaire assessed the goals of cannabis use among those who had ever used cannabis. The third questionnaire was the Schizotypal Personality Questionnaire (SPQ).

RESULTS: A Principal Components Analysis (PCA) yielded six factors accounting for 56% of the total variance. The three most powerful orthogonally rotated factors were “elevating positive moods”, “reducing negative moods” and “ease of social interaction”. Correlational analysis of these factors with the SPQ total score did not show any significant association.

DISCUSSION: These three factors seem to be comparable to the three dimensions found by others (Addington and Duchak 1997; Baigent et al. 1995; Dixon et al. 1991; Spencer et al. 2002) in clinical populations: 1) to enhance positive mood; 2) to cope with negative emotions; 3) to obtain social rewards. There is no evidence for students using cannabis to alleviate distress resulting from schizotypal traits.

DOES SEX MATTER?
A WITHIN- AND BETWEEN-SUBJECT LONGITUDINAL ASSESSMENT OF MARIHUANA'S IMPACT ON MEMORY AND PROCESSING SPEED.

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Whether marihuana produces cognitive dysfunction beyond the acute intoxication period is equivocal in large part due to methodological and interpretative limitations. A major issue when interpreting the putative impact of marihuana is the role of confounding variables including (a) factors that may covary with marihuana use that influence cognitive performance (e.g. use of other drugs, psychopathology) (b) cognitive abilities prior to the onset of marihuana use and (c) the sex of the user

In attempting to deal with these issues, researchers have identified the importance of comparison groups that are as similar on as many non-marihuana variables as feasible. For matching purposes, the optimal comparison groups would be a combination of the users prior to the initiation of regular marihuana use and a non-using group drawn from the same subject pool. The Ottawa Prenatal Prospective Study (OPPS) provides such a research possibility.

The OPPS participants, who have been evaluated since birth, are currently an average of 20 years of age. For the purposes of this report we will describe the outcomes of cognitive tests administered to these subjects when they were between the ages of 9-12 (pre-teen) and similar, age-adjusted tests when they were between 17-20 (young adults). Of the 97 subjects in the present report , approximately 20% are currently using marihuana at least 5 times per week (13 males, 6 females), 20% regularly but less than 5 joints per week (12 males, 7 females) and the remaining subjects have smoked it fewer than 3 times and have not used it in the past 3 months (29 males, 30 females). Omitted from this report due to small cell sizes are the males and females who had used marihuana regularly in the past but had not used for the previous 3 months. Current, regular use of marihuana (and other drugs) was determined by both self-report and urinalysis. A very high concordance (both in terms of sensitivity and specificity) was noted between these two measures lending considerable credence to those aspects of self-report (e.g. age of initiation of drug use) that cannot be verified by pharmacological means.

Previously we have reported, in this sample, that processing speed and various forms of memory were impacted by heavy regular use. In the present report, we examined whether cognitive functioning was differentially impacted in males and females cannabis users. After taking into account the subjects' performance in these domains prior to the initiation of marihuana use, heavy, regular marihuana use but not light use was significantly, negatively associated with immediate memory and processing speed. Neither long-term memory nor working memory was associated with heavy use. The impact of the drug was highly similar in the two sexes in all the cognitive domains considered. Critically, within some domains, the scores obtained by the heavy users were above published population norms and thus the negative impact of the drug could only be ascertained by a within-subject comparison contrasting pre- and post-drug levels of performance.

Acknowledgements: The OPPS longitudinal study is supported by NIDA

ORAL CANNABIS - EXTRACT (CE) VERSUS DELTA-9-TETRAHYDROCANNABINOL (THC) FOR PATIENTS WITH CANCER-RELATED ANOREXIA (CRA): A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY

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Purpose: CE contains many other cannabinoids beside THC, most importantly cannabidiol (CBD), modifying the effects of THC. The objective of this study was to compare the effects of CE and THC on appetite, quality of life (QoL), mood, and nausea in patients with advanced cancer and CRA.

Methods: 243 patients with advanced cancer being candidates for appetite stimulation, weight loss (≥5% during the last 6 months), and stable supportive care treatment were enrolled. After one week baseline assessments, pts were randomized (2:2:1) to 3 arms: 6 weeks bid oral CE (standardized for 2.5 mg THC and 1 mg CBD), oral 2.5 mg THC, or placebo (P). Appetite, mood, and nausea were monitored daily (diary); quality of life (EORTC-QLQ-c30), anorexia/ cachexia related symptoms (ad-hoc-module), and cannabinoid-related toxicity (ad-hoc-module; CRTox) bi-weekly.

Results: At baseline, groups were comparable in terms of age (61±12), gender (55% male), average weight loss, performance status (13% ECOG 2, 87% ECOG 0 or 1), cancer disease (80% metastatic, 68% antineoplastic treatment), appetite (33±21 [0=minimal, 100=maximal]), mood (42±21), nausea (27±24), and GHS/QoL (composite Global Health Status and overall Quality of life [EORTC-QLQ-c30 items #29 and #30]) (37±20). At present, interim data from 216/243 (89%) are available. 69/216 (32%) pts (CE 27/84, 32%; THC 26/89, 29%; P 16/43, 37%) completed the study per protocol. Increased appetite (best bi-weekly average) was reported by 72% of pts receiving CE, 55% THC, and 76% P. Intention-to-treat analysis revealed no significant differences between the 3 arms for the main efficacy parameters appetite and : GHS/QoL at week 2, 4, or 6. CRTox was not different between the three arms. Recruitment was terminated on recommendation of an Independent Review Board.

Conclusions: Oral CE at a dose of 2.5 mg THC bid is well tolerated in patients with advanced cancer and CRA with no difference in tolerability between CE and THC and placebo. No differences for appetite or GHS/QoL were found neither for CE or THC compared to P nor between CE and THC at the dose level investigated. A trend is supposed for THC to be inferior for appetite-stimulation to placebo or CE.

MAXIMALLY TOLERATED DOSE (MTD) OF STANDARDIZED CANNABIS EXTRACT IN PALLIATIVE CANCER PATIENTS: PRELIMINARY RESULTS FROM AN OPEN-LABEL, NON-RANDOMIZED PHASE I/II TRIAL

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Purpose: Delta-9-tetrahydrocannabinol (THC) is presumed to have antiemetic, appetite-stimulating, analgesic and antidepressant properties, which could be useful in the management of palliative cancer patients. Cannabis contains other cannabinoids beside THC, most importantly cannabidiol (CBD), modifying the effects of THC. The objective of this study was to determine the maximally tolerated dose (MTD) of standardized cannabis extract (CE) in patients with advanced cancer.
Methods: Patients meeting the following inclusion criteria were entered into an inpatient phase (3 weeks) and an outpatient follow-up phase (additional 49 weeks): documented advanced cancer with Karnofsky-score of ≥40%, at least two of the following symptoms: anorexia and/or chronic nausea and/or tumor pain, and/or reactive depression, and/or sleep disturbances; stable supportive care treatment. After two days of baseline assessment, patients started treatment with bid oral CE (standardized for 2.5 mg THC and 1 mg cannabidiol) and escalated the dose daily (by maximally 5 mg THC) until a target level was reached that was determined by individual body weight. For safety reasons, the first cohort consisting of three patients were allocated to a target dose of 5 mg THC/d. If no intolerable side effects (defined as 'dose-limiting events [DLEs]') occur, the next cohort would be allocated to 0.175 mg THC/kg body weight. According to the occurrence or absence of DLEs, the target dose for each next cohort was defined by the Continual Reassessment Method (CRM). This Bayesian approach uses *prior*, i.e. beforehand fixed probabilities of DLEs for each scheduled dosage. Based on these and the toxicity data of all patients observed so far, the corresponding posterior probabilities were repetitively calculated over the course of the study. A dosage was defined as intolerable if it induced DLEs in one half or more of all patients concerned. Consequently, the highest dose not meeting this criterion was regarded as MTD.
During the inpatient period, mood, nausea, appetite and global pain (on VAS); neuropathic pain and sleep disturbances (on categorical scales) were monitored daily; Quality of Life (including Global Health Status and cannabinoid-related toxicity) were monitored twice (EORTC-QLQ-C30 and complementary ad-hoc module).
Results: This is a preliminary report as final analysis is pending. Between February 2001 and May 2003, 40 patients were entered into the trial (27 women, 13 men, mean age 52.2 y); 36 patients were eligible for determining MTD which was calculated on the basis of six patients experiencing DLEs: dizziness, unsteady gait, somnolence, depersonalization, euphoria and concentration difficulty. Based on this, MTD was concluded to be 0.15 mg THC/kg body weight. Side effects were in total (no. of reports): dizziness (19), dry mouth (7), unsteady gait (5), somnolence (5), palpitations (4), loss of orientation (3), sweating (3), hallucinations (2), lack of drive (2), tiredness (2), muscle pain (2), euphoria/high (2), memory impairment, depersonalization (2), fear (2), diarrhea (2), depression (1), and muscle weakness (1). Twenty seven patients documented mood elevation on VAS in their diaries, 24 increase of appetite, 20 relief of pain, and nine relief of nausea; no patient reported on worsening of symptoms. Body weight data are available from 25 patients; nine developed an increase in body weight of > 1 kg during the three inpatient weeks, nine showed body weight increase of < 1 kg; four patients had stable body weight, and three patients lost weight during this time.
Conclusions: Oral standardized cannabis extract has been shown to be tolerated well at a MTD of 0.15 mg THC/d/kg body weight by patients with advanced cancer. Though preliminary and of restricted validity as it lacks a control group, cannabis extract seems to give useful symptom control in the palliative care setting which has to be verified in controlled clinical trials.

CANNABIS VAPORIZER COMBINES EFFICIENT DELIVERY OF THC WITH EFFECTIVE SUPPRESSION OF PYROLYTIC COMPOUNDS

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Cannabis vaporization is a technology aimed at delivering inhaled cannabinoids while avoiding the respiratory hazards of smoking by heating cannabis to a temperature where therapeutically active cannabinoid vapors are produced but below the point of combustion where noxious pyrolytic byproducts are formed.

This study was designed to evaluate the efficacy of an herbal vaporizer known as the Volcano®, produced by Storz & Bickel GmbH&Co. KG, Tuttlingen, Germany (http://www.storz-bickel.com. Three 200-mg samples of standard NIDA cannabis were vaporized at temperatures of 155° - 218° C°. For comparison, smoke from combusted samples was also tested.

The study consisted of two phases: (1) a quantitative analysis of the solid phase of the vapor using HPLC-DAD-MS (High Performance Liquid Chromatograph - Diode Array -Mass Spectrometry) to determine the amount of cannabinoids delivered; (2) a GCMS (Gas Chromatograph Mass Spectrometry) analysis of the gas phase to analyze the vapor for a wide range of toxins, focusing on pyrene and other polynuculear aromatic hydrocarbons. (PAHs).

The HPLC analysis of the vapor found that the Volcano delivered 36%-61% of the THC in the sample, a delivery efficiency that compares favorably to that of marijuana cigarettes.

The GCMS analysis showed that the gas phase of the vapor consisted overwhelmingly of cannabinoids, with trace amounts of three other compounds. In contrast, over 111 compounds were identified in the combusted smoke, including several known PAHs.

The results indicate that vaporization can deliver therapeutic doses of cannabinoids with a drastic reduction in pyrolytic smoke compounds. Vaporization therefore appears to be an attractive alternative to smoked marijuana in future medical cannabis studies.

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A SUPPOSITORY FORMULATION FOR DELIVERY OF Δ^9-THC USING A PRODRUG

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Δ^9-THC has been formulated in a sesame seed oil soft gelatin capsule and market as Marinol®, which is approved by the USFDA as antimetric for cancer patients receiving chemotherapy and as an appetite stimulant for AIDS patients. The lack of consistent bioavailability and the problems associated with the first pass effect from this formulation necessitated the search for other alternative formulation(s). One such formulation with possibility for overcoming the difficulties associated with the oral preparation in suppositories. However, Δ^9-THC has been reported to lack bioavailability from suppositories (from either lipophylic or hydrophylic bases). Therefore, a prodrug had to be developed to effect rectal bioavailability. Δ^9-THC-hemisuccinate (THC-HS) was found to be the ideal prodrug. Formulation of THC-HS in lipophylic bases was necessary for stability reasons. The THC-HS suppositories were studies in monkeys and dogs and showed promising bioavailability data. This prompted further development of the formulation and much data were generated in humans.

This presentation will summarize the different animal and clinical bioavailability data and the advantages this suppository formulation has over Marinol® in effecting delivery of Δ^9-THC.

URINE LEVELS OF 11-NOR-DELTA-9-TETRAHYDROCANNABINOL-9-CARBOXYLIC ACID IN PARKINSON´S DISEASE PATIENTS USING CANNABIS

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In our previous questionnaire-based study, we have shown cannabis use seems to improve the symptoms of Parkinson´s disease, namely bradykinesia. The alleviation of PD symptoms was significantly more often reported by patients using cannabis consistently long-term (3 months or more).

We have analysed urine from seven patients who had taken cannabis consistently long-term (more than one year) and a single patient who had only taken it inconsistently one day before analysis. We have performed gas chromatography/mass spectrometry (GC/MS) analysis (ion 371 m/z was monitored in silylated 11-nor-delta-9-THCOOH) on ion trap spectrometer after previous extration on SPEC-C18-I Cartridges.

In the group of seven patients who were using cannabis consistently over several months, an effect of urine level of 11-nor-delta-9-THCOOH (major delta-9-THC metabolite in the urine) on bradykinesia and rigidity was apparent. Thus, all regular users having 11-nor-delta-9-THCOOH concentrations in urine above 50 ng/ml (4/7) reported significant improvement in bradykinesia and/or rigidity. In contrast, in patients where 11-nor-delta-9-THCOOH levels were lower than 50 ng/ml (3/7) there was no reported improvement in either. Interestingly, one patient who was not a regular cannabis but who had taken cannabis one day before analysis the urine levels of 11-nor-delta-9-THCOOH were high (132.2 ng/ml) but no improvement in symptoms was reported, a finding consistent with the conclusions of the questionnaire, that chronic use of cannabis might be required to obtain a subjective improvement in symptoms.

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POSSIBLE USE OF ENDOCANNABINOID-BASED THERAPEUTIC DRUGS AGAINST TUMOUR GROWTH AND METASTATIC SPREADING

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Evidence has been accumulating in the past five years suggesting that the endogenous ligands of cannabinoid receptors, the endocannabinoids, and particularly anandamide and 2-arachidonoyl-glycerol (2-AG), which appear to be ubiquitous in animal tissues, can influence the decision of the cell to survive, and hence proliferate or differentiate, or to die. Starting from early evidence that Δ^9-tetrahydrocannabinol, as well as other phytocannabinoids, can inhibit the proliferation of cancer cells, we and others have investigated whether, and through what mechanism, anandamide and 2-AG inhibit tumour growth. The results so far obtained can be summarized as follows:

- Endocannabinoids inhibit the growth factor (prolactin, NGF, etc.)-dependent proliferation of human breast and prostate cancer cells in vitro. These effects are due to suppression of the expression of receptors (prolactin long form receptor, *trk*, etc.) for these growth factors, which in turn is exerted via activation of cannabinoid CB_1 receptors, and subsequent sustained inhibition of protein kinase A, and/or stimulation of the MAP kinase pathway;
- A metabolically stable analogue of anandamide inhibits the proliferation of rat thyroid carcinoma cells, both in vitro and in vivo, after intra-tumour administration, again by activating CB_1 receptors, and by inhibiting the activity of the K-*ras* oncogene product;
- Endocannabinoids inhibit the proliferation of human colorectal carcinoma cells by activating preferentially (but not only) the CB_1 receptor;
- THC and synthetic cannabinoids inhibit the growth of glioma and astrocytoma cells, both in vitro and in vivo, after intra-tumour administration, by activating preferentially the cannabinoid CB_2 receptor, and hence producing a sustained stimulation of ceramide formation, which in turn causes apoptosis of cancerous, but not healthy, glial cells;
- THC and synthetic cannabinoids inhibit the growth of lymphoma cells both in vitro and in vivo by activating the CB_2 receptor;
- THC and synthetic or endogenous cannabinoids inhibit angiogenesis in gliomas, skin tumours and thyroid carcinomas by activating both CB_1 and CB_2 receptors and suppressing the expression of both VEGF and its receptors;
- A metabolically stable analogue of anandamide, administered i.p. at a very low dose, inhibits the metastasis of Lewis lung carcinoma cells in mice in vivo.

It has also been shown that the levels of endocannabinoids and of their receptors can change in some tumours and cancer cells, both in vivo and in vitro, as compared to the corresponding healthy tissues and cells. This observation, together with the finding that substances that selectively enhance the endogenous levels of the endocannabinoids by inhibiting their inactivation, also inhibit cancer growth in vitro and in vivo, suggests that endogenous anandamide and 2-AG might tonically control cancer cell growth.

In summary, on the basis of these recent developments, it does not seem too farfetched to hypothesise the future use as anti-cancer agents of substances that activate the cannabinoid receptors, either directly or indirectly, by enhancing endocannabinoid levels. In this latter case, these novel drugs are likely to produce much more tolerable side-effects than "direct" CB_1 receptor agonists. Such side effects are also likely to be negligible upon repeated intra-tumour administration of low doses of CB_1 receptor agonists. However, the immune-suppressing effects of cannabinoid receptor agonists may represent a potential draw-back of these endocannabinoid-based anti-cancer therapies.

ANALGESIC EFFECTS OF 1`,1`DIMETHYLHEPTYL-DELTA8-THC-11-OIC ACID (CT-3) ON CHRONIC NEUROPATHIC PAIN IN MAN.

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Ajulemic acid (CT-3), a potent analog of THC-11-oic acid, produces marked anti-allodynic and analgesic effects in animals without evoking any of the typical effects as described in models of the psychotropics actions of cannabinoids. Therefore CT-3 may work as analgesic in resistant neuropathic pain which is poorly controlled.

Methods: Twenty-one patients with chronic neuropathic pain were randomized to two 7-day treatment orders in a crossover design. They received either 20 or 40 mg CT-3 (n=10) or placebo (n=11) twice a day during the first treatment week, then vice versa in the second treatment week. Visual analog scores (VAS) and verbal rating scales (VRS) for pain, vital signs including blood tests and ECG, as well as the Trail Making Test (TMT) and Addiction Research Center Inventory-Marijuana (ARCI-M) were measured.

Results: Pain scores as measured by VAS at improved significantly, transit dry mouth and tiredness were reported significantly more often than in the placebo treatment week There were no significant differences among the treatment groups with respect to vital signs, TMT and ARCI-M.

Conclusion: CT-3 was effective in reducing chronic neuropathic pain when compared to placebo. No adverse psychological or major physical effects were observed.

AN ESCALATING DOSE STUDY OF CANNADOR FOR POSTOPERATIVE PAIN: DOSE RELATED EFFECTS

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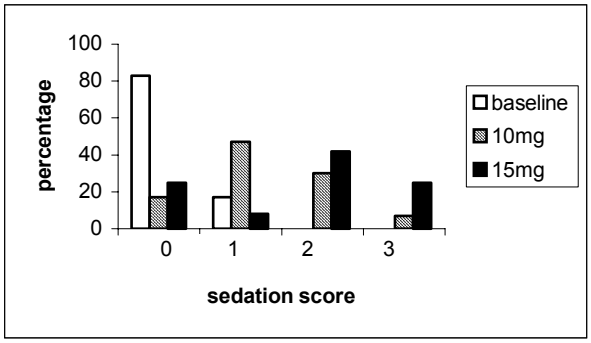
Cannador is a standardized oral pharmaceutical preparation of cannabis containing the plant cannabinoids tetrahydrocannabinol (THC) and cannabidiol. It is hypothesized that exogenous cannabinoids may modulate pain sensations because endogenous cannabinoids in animals demonstrate antinociceptive activity. The capsules of Cannador are supplied under UK Home Office Licence and with Medicines Control Agency approval. This open-label study aimed to determine the effect of increasing doses on pain relief and side effects following the administration of a single dose in postoperative patients. The dose of Cannador used was based on the THC content and three sequential groups of patients received either 5mg, 10mg or 15mg.

Patients were recruited preoperatively after Ethics Committee approval and informed written consent if it was anticipated that a morphine-based patient controlled analgesia (PCA) system was to be prescribed postoperatively. Once oral medication was feasible and the patient agreed to stop the PCA, the study began. Baseline assessments and confirmation of eligibility were checked. Capsules of 2.5mg Cannador were then administered as a single dose. Pain relief, side effects and time to rescue medication were measured and recorded over 6 hours after drug administration. The 5mg dose was used in the first group of patients and then the dose was increased depending on the number of patients who required rescue analgesia.

Rescue analgesia was required in all patients in the 5mg group (n = 11) compared with 50% (n = 30) and 33% (n = 16) in the 10mg and 15mg groups respectively. The time to rescue analgesia was longer in the 10mg group compared with the 5mg dose group (P = 0.003) but not when compared with the 15mg dose group. Sedation increased during the study period in the 10mg and 15mg groups as shown in the Figure, and the incidence of mood changes increased from 0% to 40% at 10mg and 70% at 15mg. These results demonstrate dose related pain relief and adverse effects.

Figure: Percentage of patients after 10mg and 15mg Cannador with sedation scores recorded at baseline and at maximum effect. (Scores: 0 = none, 1 = mild, 2 = moderate sedation, 3 = asleep)



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THE EFFECTS OF SMOKED CANNABIS IN PAINFUL PERIPHERAL NEUROPATHY AND CANCER PAIN REFRACTORY TO OPIOIDS

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INTRODUCTION: There is significant evidence that cannabinoids may be involved in the modulation of pain, especially of neuropathic origin. There is also theoretical rationale to suggest that cannabinoids may provide synergistic analgesia with opioids while possibly reducing opioid-related side effects. No information is available on potential pharmacokinetic interactions between cannabinoids and opioids.

METHODS: We are currently conducting two clinical trials of smoked marijuana in two populations of patients with pain: HIV patients with painful peripheral neuropathy and cancer patients with persistent pain despite an opioid analgesic. Both studies are designed to begin with a 16 patient open-label pilot proof-of-concept phase. If effectiveness is demonstrated in the pilot, the magnitude of the effect allows us to calculate a follow-on randomized, double-blind controlled trial of smoked marijuana vs smoked placebo. In addition to the effect of smoked marijuana on the subjects' chronic clinical pain, we are also evaluating the impact on an experimental heat/capsaicin pain model. Here we report experience with the open label phase of the neuropathy study.

RESULTS: Sixteen subjects (14 men, 2 women, mean age 43 years) completed the HIV neuropathy pilot trial. Patients had an average of 6 years of neuropathic pain. In 3 cases the pain was felt to be secondary to HIV alone, in 8 secondary to dideoxynucleoside antiretrovirals and to both in 5. Excellent correlation was seen between the response to smoking in the effect on both the chronic neuropathic and the acute experimental pain model over a six-hour period. Overall 10 of the 16 participants experienced a greater than 30% reduction in their neuropathic pain after seven days. This allowed us to proceed with our currently enrolling randomized placebo-controlled trial with a target sample size of 50 subjects. Additional controlled trials of smoked marijuana for HIV peripheral neuropathy are being conducted by other University of California Center for Medicinal Cannabis Research investigators.

CONCLUSION: Preliminary results from a small, uncontrolled trial of smoked marijuana in HIV peripheral neuropathy are encouraging. The ongoing randomized trials will better elucidate the role of cannabinoids in this condition. A heat/capsaicin experimental pain model appears to be a good predictor of response to chronic pain. The potential of a beneficial clinical interaction between cannabinoids and opioids requires further study.

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ENDOGENOUS CANNABINOIDS AND THEIR ROLE IN PSYCHIATRIC DISORDERS

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The recent discovery of the endogenous cannabinoid system reveals new perspectives regarding the role of this system in the pathogenesis of schizophrenia. This new study in the field investigated the specific role of the endocannabinoid system in different psychiatric disorders.
Method: About 220 healthy volunteers and patients suffering either from schizophrenia, affective disorders or dementia were clinically investigated. Endogenous cannabinoids were studied in cerebrospinal fluid and plasma of these subjects and correlated to clinical symptoms.
Findings: Cerebrospinal concentrations of specific endogenous cannabinoids were significantly higher in schizophrenic patients never treated with neuroleptics than in healthy controls. These findings were specific for patients suffering from schizophrenia.
Conclusions: Endogenous cannabinoid levels in cerebrospinal fluid are specifically elevated in schizophrenic patients. This may reflect an imbalance in endogenous cannabinoid signaling, which may be either a specific reaction to or a pathophysiological condition in schizophrenia itself.

Leweke FM, Giuffrida A, Wurster U, Emrich HM, Piomelli D (1999) Elevated endogenous cannabinoids in schizophrenia. NeuroReport 10: 1665-1669

CANNABIDIOL, Δ^9-TETRAHDYROCANNABINOL, AND CANNABICHROMENE EXTRACTS ALTER BEHAVIORAL DESPAIR ON THE MOUSE TAIL SUSPENSION TEST OF DEPRESSION

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Several investigators have speculated that cannabis use has been used for self-medication of depression (Degenhardt & Lynskey, Soc. Psychiatry. Psychiatr. Epidemiol., 2000, 36, 219; Diego & Sanders, Adolescence, 2001, 36, 491; Tunving, ACTA Psychiatr. Scand., 1985, 72, 209). To test this hypothesis, cannabis extracts containing Δ^9-tetrahydrocannabinol (THC), cannabidiol (CBD) or cannabichromene (CBC) were tested for antidepressant effects.

Behavioral Method. Each mouse was suspended from a bar by the tail using adhesive tape. The total number of movements, total amount of time spent immobile and amplitude of struggling were measured for six minutes. Immediately after the tail suspension test, each mouse was individually placed in the open-field chamber for five minutes. Activity, rearing, grooming and defecation rates were recorded. Antidepressant effects are indicated by an increase in the frequency of struggling (activity) or decrease in activity (immobility) during the test.

Animals and Drugs. Animals were C57Bl6J mice, obtained from Jackson Laboratories. Drug groups were: **THC extract:** 0, 0.5, 1, 2, 4 or 8 mg/kg or 30 mg/kg of imipramine **CBD extract** 0, 5, 10, 20, 40 or 80 mg/kg CBD extract or 30 mg/kg of imipramine. **THC+CBD mixture**, 0 mg/kg, 4 mg THC + 0.59 mg CBD (8:1 group), 2 mg THC + 20 mg CBD (1:10 group) and 4 mg THC + 20 mg CBD (1:5 group) **CBC extract** 0, 5, 10, 20, 40 or 80 mg/kg or 30 mg/kg of imipramine. All drugs were injected intraperitoneally 30 minutes before testing on the tail-suspension test.

Results. THC at dosages of 4 mg and 8 mg produced significant reductions in the number of movements and significant increases in the amount of time spent immobile (4 mg mean time immobile=273.8 sec., SD= 112.9; 8 mg mean time immobile=268.3 sec., SD= 58.6) relative to vehicle treated controls (mean time= 194.106 sec., SD=70.460). CBD produced behaviors that were consistent with imipramine (i.e., elevated activity: 20 mg CBD dose mean= 985.9 sec., SD=404.9 sec.; control mean= 550.3 sec., SD=467.2 sec.; imipramine 1171.5 sec., SD 623.2). Moderate doses of CBC produced behaviors that were consistent with imipramine on the tail suspension test (i.e., elevated activity: 40 mg CBC dose mean= 916.1 sec. control mean= 462.5 sec., SD=467.2 sec.; imipramine dose mean 733.5 sec.). Also, the amplitude of the struggling behavior was higher in the animals administered CBC. The percentage of animals making large amplitude responses was recorded. Statistically significant increases in amplitudes of struggling were found between vehicle controls (mean=13.3.%), the 20 mg CBC dose mean=31.4%) and the 80 mg CBC dose (mean=30.2%). Imipramine was also statistically significant (mean=23.8%).

Discussion. On the basis of this animal model, these data are the first to indicate that CBD and CBC have therapeutic potential in relieving depression. These data also support the hypothesis that cannabinoids have differential modes of action.

Extracts were supplied by GW Pharmaceuticals.

PHARMACOKINETICS AND –DYNAMICS OF PULMONAL AND INTRAVENOUS Δ^9-TETRAHYDROCANNABINOL (THC) IN HUMANS

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Cannabis is widely used in folk medicine to relieve pain. Analgesia could not be confirmed in our previous pain study with healthy subjects using oral THC (dronabinol, Marinol®). Extensive liver first pass metabolism and THC plasma peaks varying between 30 and 120 min were observed. The aim of the present study was to develop an inhalation solution of THC, to acquire pharmacokinetic profiles of pulmonal and intravenous (i.v.) THC, and to compare the analgesic effect of the inhalation solution vs. placebo.

Eight healthy volunteers (4 female, 4 male) were included in the randomised, placebo controlled, double-blind, crossover study. Two aqueous, physiologically well tolerable formulations were prepared using a solubilisation technique. I.v. THC (0.053 mg/kg b.wt.), pulmonal THC (0.053 mg/kg b.wt.), or a placebo inhalation solution were administered as single doses. The inhalation solution was nebulised with a pressure-driven, commercially available nebuliser device. At defined time points blood samples were collected, somatic and psychotropic side effects (visual analog scales) and vital functions (blood pressure, heart rate, and oxygen saturation) monitored, and an ice water immersion test was performed to measure analgesic effects.

Peak plasma levels of THC and its main metabolites 11-hydroxy-THC and 11-carboxy-THC after pulmonal administration were 22.62 ± 6.92 ng/mL (mean ± SEM), 1.83 ± 0.47 ng/mL, and 13.89 ± 2.94 ng/mL, respectively. The bioavailabilty of the pulmonal THC was 28.6 ± 8.2 %. The side effects observed in the inhalation session were coughing and slight irritation of the upper respiratory tract during the inhalation (reversible within 30 min, partly imparing inhalation efficiency), very mild psychotropic effects, and headache. The side effects after i.v. THC were much more prominent, also showing strong psychotropic symptoms, increased heart rate, and dry mouth. Neither pulmonal nor i.v. THC did significantly reduce pain in the ice water immersion test.

In conclusion, this study shows that pulmonal THC produced peak plasma levels within minutes after inhalation. Due to reduced liver first pass metabolism the bioavailability was much higher compared to oral THC. However, the analgesic potency of THC in our pain model could not be increased by the better bioavailability of the pulmonal application form.

EVALUATION OF A GC/MS PROCEDURE FOR THE ANALYSIS OF Δ^9-THC AND Δ^9-THC-HEMISUCCINATE IN SUPPOSITORY FORMULATIONS AS PART OF A STABILITY STUDY

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Δ^9-THC-hemisuccinate has been formulated in suppositories to effect consistent bioavailability of Δ^9-THC. Animal data as well as clinical data proved the efficacy of the formulation in delivering Δ^9-THC with clear advantages over oral THC preparation already on the market (Marinol®). The development of the suppository formulation necessitated the selection of a base that would provide the most bioavailability and best stability (shelf-life). Lipophilic bases were found to be the most suitable.

In this report a GC/MS procedure was developed and compared with the HPLC method originally used to study the stability of Δ^9-THC-hemisuccinate ester in lipophilic bases.

The method is based on partitioning (by vortexing for 30 seconds) of portions of the suppositories with MeOH at a temperature sufficient to melt the base followed by removal of the bulk of the extracted base by quick freezing of the extraction tube by immersion in dry ice/acetone bath and separation of the methanolic extract by filtration through a small cotton plug. An internal standard (Δ^9-THC-hemiglutarate) was added to each sample prior to extraction. The methanolic solution is then analyzed directly by HPLC (C_{18} column with MeOH : H_2O : Acetic acid (80:20:0.01) solvent system and UV detection at 220 nm. Another portion of the methanolic extract was evaporated and derivatized (TMS) and used for the GC/MS analysis (15m x 0.25mm DB-1 column, 0.25µ film operated at 150°C (1 min) to 250°C @ 10°C/min with a 10 min hold @ 250°C) in the SIM mode. The ions monitored were at m/z 371, 303 and 386 for Δ^9-THC, 173, 297 and 313 for the hemisuccinate and 187, 297 and 313 for the hemiglutarate (I.S.), with the quantitation ions underlined. Ion ratios were used for peak identification and calibration curves were prepared from 0.1 to 0.5 mg/g of THC (r ranged from 0.9483 to 0.9999) and 1 – 5 mg/g of the hemisuccinate (r ranged from 0.9947 to 0.9993) for the different bases.

The method was used to quantitate Δ^9-THC and Δ^9-THC-hemisuccinate in suppositories prepared in difficult bases, namely Suppocire NAO, Wecobee M, Paraffin mix and Whitepsol-H15 as part of ongoing stability study using an HPLC method.

The GC/MS and HPLC data were found to be in agreement, with correlation coefficients ranging from 0.8588 to 0.9994 for Δ^9-THC and from 0.9497 to 0.9996 for hemisuccinate ester for the different bases.

Work is in progress to implement the use of deuterated internal standards for both Δ^9-THC and Δ^9-THC-HS to further improve on the method. d_9-Δ^9-THC and d_4-Δ^9-THC-HS will be used as the internal standards for the GC/MS analysis. The use of Δ^9-THC-hemiglutarate in this study was designed to allow direct comparison between the GC/MS method and the HPLC method.

CHRONIC PERIPUBERTAL CANNABINOID TREATMENT LEADS TO BEHAVIOURAL DISTURBANCES IN ADULT RATS

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The present study tested the hypothesis that chronic treatment with cannabinoids causes specific and persistent behavioural alterations in adult rats only after treatment during peripubertal development.

Chronic treatment with the synthetic full cannabinoid agonist WIN 55,212-2 (WIN) (1,2 mg/kg) or vehicle was extended over 25 days either throughout the rats puberty (postnatally day (pd) 40 - 65) or for a similar time period in adult rats (pd > 70). The rats received 20 injections intraperitoneally (i.p.). Adult rats were tested for object recognition memory, performance in a progressive ratio (PR) operant behaviour task, food preference, locomotor activity and on prepulse inhibition (PPI) of the acoustic startle response (ASR).

PPI was significantly disrupted only by peripubertal cannabinoid treatment on pd 85, 120 and still on pd 150. This longlasting PPI deficit was reversed by the acute administration of the dopamine antagonist haloperidol. Furthermore, we found deficits in recognition memory of pubertal treated rats and these animals showed lower break points in a PR schedule. Adult chronic cannabinoid treatment had no effect on PPI, object recognition and the performance in a PR schedule of reinforcement. Chronic WIN treatment had no effect on food preference or total food intake and on locomotor activity.

Therefore, we conclude that puberty in rats is a vulnerable period for adverse effects of cannabinoid treatment. The endogenous cannabinoid system seems to be highly susceptible to cannabinoid administration during this developmental phase, as evidenced by the disruption of sensorimotor integration, mnemonic and motivational processes.

There is evidence from recent studies for a connection between schizophrenia and cannabis use. Since PPI and object recognition memory are impaired in schizophrenic patients and since the PR schedule might serve as an animal model for anhedonia, we propose chronic cannabinoid administration during pubertal development as an animal model for at least some aspects of schizophrenia. Evidence for this assumption is also given by the fact that the cannabinoid-induced PPI deficit observed in our study was reversed by a clinically potent antipsychotic drug.

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